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Recurrent Episodes of Rhabdomyolysis after Seizures in a Patient with Glycogen Storage Disease Type V

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Dear Editor,

Glycogen storage disease type V (GSD-V) is the most common disorder of muscle glycogenosis and is caused by alterations in the *PYGM* gene.[1] Patients with GSD-V typically present with exercise intolerance, episodic rhabdomyolysis, and the second-wind phenomenon. Seizure has been well described as a provocative event for rhabdomyolysis, but it is not classical feature of GSD-V. Here we report recurrent episodes of rhabdomyolysis after seizures in a Korean patient with *PYGM* mutations.

The male proband (II-2 in Fig. 1A) was the first child of nonconsanguineous healthy parents. He achieved normal motor milestones. At the age of 17 years he was hospitalized for rhabdomyolysis with a serum creatine kinase (CK) level of 718,000 IU/L after intense exercise and generalized tonic-clonic seizure (Supplementary Table 1 in the online-only Data Supplement). He did not have fixed muscle weakness. An electromyography study showed no spontaneous activities. Electroencephalography demonstrated a few spikes at the left frontocentral region. He was hydrated, and treated with anticonvulsants, but the serum CK level remained elevated (630 IU/L) at rest. The ischemic forearm exercise test demonstrated no increase in serum lactate level and a normal increase in serum ammonia level. At the age of 18 years he was readmitted to our clinic due to rhabdomyolysis and seizure. His serum CK level was 486,800 IU/L. Subtle muscle weakness was initially found in the shoulder girdle muscles, but recovered after 3 days. At the age of 28 years he was hospitalized for the third event of rhabdomyolysis (serum CK level: 124,500 IU/L) after a seizure. We performed targeted sequencing of 69 myopathy-related genes, including *PYGM* (Supplementary Table 2 and 3 in the online-only Data Supplement). DNA fragments in the target regions were enriched by solution-based hybridization capture, followed by sequencing with the Illumina Hiseq2000 platform. The sequencing data were analyzed using a standard pipeline (see in Supplementary Information in the online-only Data Suplement). Variants were then filtered further based on the patient's phenotype. We identified compound heterozygous *PYGM* mutations of c.1531delG and c.1999A>T (Fig. 1B). The c.1531delG mutation has been reported previously,[2] but the c.1999A>T mutation is novel, since it was not detected in dbSNP138 or the 1000 Genomes Database (September 2014 release). *In silico* predictions support a deleterious effect of the c.1999A>T mutation on *PYGM* (Supplementary Table 4 in the online-only Data Supplement). Additionally, genomic evolutionary rate profiling indicated that the affected nucleotide is highly conserved (score=4.91) (Fig. 1C). Thus, we determined that the c.1531delG and c.1999A>T compound heterozygous *PYGM* mutations were the underlying cause of the observed myopathy. A deltoid muscle biopsy was performed at the age of 18 years. Light microscopy of the sample with hematoxylin and eosin staining revealed moderate variations of fiber size and shape as well as numerous scattered markedly necrotic myofibers with macrophage infiltration (Fig. 1D). The periodic acid-Schiff stain showed a slightly increased positive reaction in the remaining myofibers. Electron microscopy re-

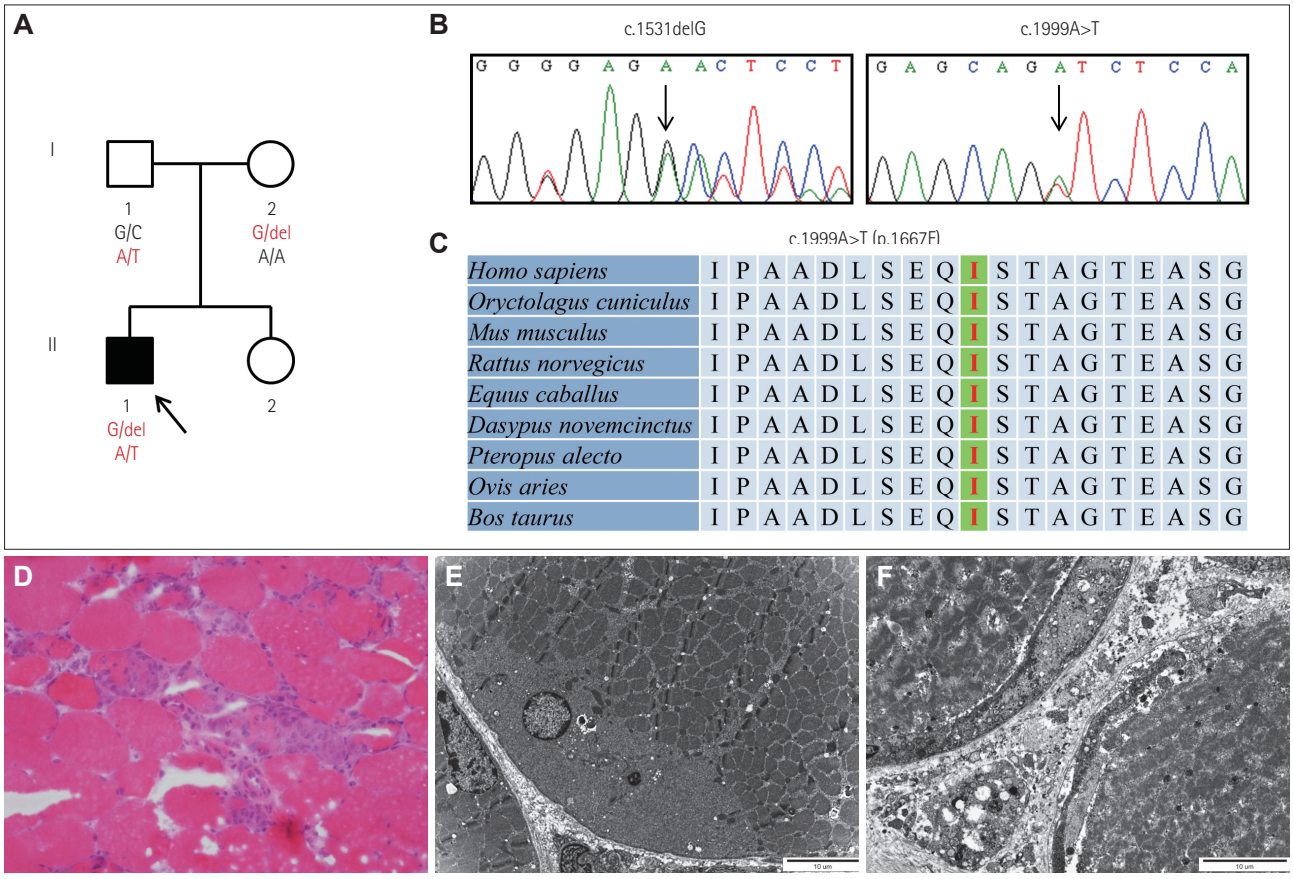

Fig. 1. Pedigree, sequencing chromatograms, conservation profile, and pathology. A: Pedigree of a Korean patient with compound heterozygous *PYGM* mutations. Arrows indicates the proband (square: male; circle: female; filled: affected; and nonfilled: unaffected). B: Sequencing chromatograms of *PYGM* mutations c.1531delG (p.D511fs) and c.1999A>T (p.I667F). Arrows indicate mutation sites. C: Conservation analysis of the amino acid sequence at the p.I667F mutation site, which was well conserved among the subset of species studied. D, E, and F: Histopathologic examination of a deltoid muscle. D: Hematoxylin and eosin (H-E) stain revealed moderate variations of fiber size and shape, and the presence of many scattered necrotic myofibers with macrophage infiltration. E and F: Electron microscopy revealed focal subsarcolemmal accumulation of glycogen (E) and necrotic myofibers exhibiting variable stages of degenerative changes (F) (D: H-E stain, ×200, E: EM, ×6,000, F: EM, ×7,000).

vealed the focal subsarcolemmal accumulation of glycogen (Fig. 1E) and necrotic myofibers exhibiting variable stages of degenerative changes (Fig. 1F).

We have identified compound heterozygous *PYGM* mutations (c.1531delG and c.1999A>T) using targeted sequencing of 69 myopathy-related genes. GSD-V is caused by a deficiency of the muscle isoform of phosphorylase, which is encoded by *PYGM*. Human phosphorylase consists of three isoforms that are differentially expressed in the muscle, brain, and liver, with the muscle isoform being mainly expressed in muscle tissue. Therefore, GSD-V is usually considered to be a pure myopathy. However, both the brain and muscle isoforms were expressed in astrocytes, which predominantly contain glycogen in the adult brain.[3] The occurrence of seizures has rarely been reported in patients with GSD-V,[1,4] which suggests that the muscle isoform has an additional role in the brain; however, the precise nature of this role remains to be determined.

In conclusion, this is the first report of novel compound heterozygous *PYGM* mutations in a Korean patient with recurrent seizure as rare provocative events of rhabdomyolysis.

Supplementary Materials

The online-only Data Supplement is available with this article at http://dx.doi.org/10.3988/jcn.2016.13.3.373.

Conflicts of Interest

The authors have no financial conflicts of interest.

REFERENCES

1. Quinlivan R, Buckley J, James M, Twist A, Ball S, Duno M, et al. McArdle disease: a clinical review. *J Neurol Neurosurg Psychiatry* 2010;81:1182-1188.
2. Park HJ, Shin HY, Cho YN, Kim SM, Choi YC. The significance of clinical and laboratory features in the diagnosis of glycogen storage disease type V: a case report. *J Korean Med Sci* 2014;29:1021-1024.

3. Pfeiffer-Guglielmi B, Fleckenstein B, Jung G, Hamprecht B. Immunocytochemical localization of glycogen phosphorylase isozymes in rat nervous tissues by using isozyme-specific antibodies. *J Neurochem* 2003;85:73-81.

4. Walker AR, Tschetter K, Matsuo F, Flanigan KM. McArdle's disease presenting as recurrent cryptogenic renal failure due to occult seizures. *Muscle Nerve* 2003;28:640-643.